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ID

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
09/181,311	10/28/98	LEE	A	APV-382.01

HM12/0816

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EXAMINER	
TURNER, S	
ART UNIT	**PAPER NUMBER**
1647	11

DATE MAILED: 08/16/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/181,311	Lee et al
Examiner	**Group Art Unit**
Sharon L. Turner, Ph.D.	1647

☒ Responsive to communication(s) filed on 5-22-00

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-30 is/are pending in the applicat

Of the above, claim(s) 1-6 and 10-30 is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 7-9 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claims 1-30 are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Group and/or Art Unit of U.S. Patent application SN 09/181,311 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Technology Center 1600, Art Unit 1647.

Sequence Requirements

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Full compliance with the sequence rules is required in response to this office action.

Alternatively, if the sequences are already in compliance, applicant should amend the specification and Figures to refer to all sequences by SEQ ID NO:, see in particular 6, 9 and the brief description of the drawings.

Priority

3. If applicant desires priority under 35 U.S.C. 119(e) based upon a previously filed provisional application, specific reference to the earlier filed application(s) must be made in the instant application. This should appear as the first sentence of the specification following the title, preferably as a separate paragraph. The status of nonprovisional parent application(s) (whether patented or abandoned) should also be included. If a parent application has become a

patent, the expression "now Patent No._____" should follow the filing date of the parent application. If a parent application has become abandoned, the expression "now abandoned" should follow the filing date of the parent application.

Election/Restriction

4. Applicant's election with traverse of Group II in Paper No. 10 is acknowledged. The traversal is on the ground(s) that no undue burden is imposed on the examiner to search all groups. This is not found persuasive because there is an undue burden on the examiner for search and examination of all claims as evidence by their different classification, structural and functional characteristics and method steps. There is no expectation that a search for any group would encompass a search for any other group.

The requirement is still deemed proper and is therefore made FINAL.

5. Newly submitted claims 12-21 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: the claims are no longer drawn to the same functional activity, previously regulating proliferation or migration, but are now drawn to genes which are upregulated or downregulated during differentiation which differs from the function of an agent which modulates this response.

Since applicant has received an action on the merits for the originally presented invention drawn to identifying genes, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 12-22 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

6. Claims 1-6 and 10-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 7-9 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial, credible asserted utility or a well established utility.

The specification at p. 2, lines 11-32 teach that the invention is directed to an *in vitro* system for rapidly and uniformly inducing immortalized neural crest cells to smooth muscle cell differentiation. The specification further teaches that the invention is also directed to methods for treating or preventing arteriosclerosis by inhibiting or regulating the activity of smooth muscle differentiation by administration of the compounds that inhibit or regulate the nodal regulators identified from use of this *in vitro* system, such compounds being useful in the treatment of vascular trauma, vascular surgery, transcatheter vascular therapy, vascular grafting, placement of a vascular shunt or intravascular stent, in addition to the treatment of vascular and cardiovascular indications characterized by decreased lumen diameter, e.g., coronary heart disease, neoplasms, uterine fibroid, and other vascular and endothelial disorders.

Such utilities do not constitute either specific and substantial, credible utilities because the uses and claimed methods merely rely on the relevant knowledge of the skilled artisan to perform routine experimentation to determine up-regulation and down-regulation of genes in cells which utilize the inherent properties of any nucleic acid to hybridize (bind) and encode. Thus, the methods and research steps merely constitute research and reagents utilized by the skilled artisan to perform further experimentation to discover a "real-world" use of the specified *in vitro* system. The recited uses also do not constitute a credible or well-established utility because the invention does not disclose specific and substantial uses for any particular identified sequence using the general experimental method. In addition, the specification does not teach any method for determining the use of the identified compounds which are modulated during neural crest cell smooth muscle differentiation. As recognized by Skolnick et al., Trends in Biotech., 18(1):34-39, 2000 and Bork P., Genome Research 10:398-400, 2000, the skilled artisan is well aware that there is an unpredictable nature in the ability of encoding nucleic acids to predict structural and functional activities for any particular protein or protein family, and that even when highly homologous and conserved residues are known only experimental research can confirm the artisan's best guess, see in particular Skolnick, abstract and Box 2, and Bork, Limitations of Gene Expression Data Extrapolations. Thus, for these reasons there is no specific and substantial, credible asserted utility or well-established utility for the claimed method of determining gene regulation.

Claims 7-9 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial, asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In addition to the aforementioned, the following defects are noted with respect to enablement of instant invention as claimed.

The specification and claims do not teach SM22α, levels or time periods of induction such that the skilled artisan can determine if SM22α is induced in cells as claimed, i.e., such that SM22α is induced for a time period sufficient for the neural crest cells to begin differentiation into smooth muscle cells and thus the skilled artisan can not readily make and use the culture system. In additon required elements for such induction appear absent. For example, Jain et al., J. of Biol. Chem., 273(11):5993-5996, March 13, 1998, teach that Monc-1 cells require addition of M199, supplemented with 10% FBS, penicillin, streptomycin and HEPES is required for SMC differentiation, see in particular p. 5993, column 1, Cell Culture and Reagents whereas Shah et al., Cell, 85:331-343, May 3, 1996 teach that neural crest stem cells require BMP2 and TGFβ1 for αSMA induction and differentiation to smooth muscle cells. Thus, the skilled artisan is unable to determine without further direction those requirements necessary for SM22α induction and differentiation of neural crest cells to smooth muscle cells.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 7-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The specification and claims do not teach the metes and bounds of SM22α, level or time period of induction such that the skilled artisan can determine if SM22α is induced in cells and such that SM22α is induced for a time period sufficient for the neural crest cells to begin differentiation into smooth muscle cells and thus the skilled artisan can not readily determine the metes and bounds of the claims.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

12. Claim 7 is rejected under 35 U.S.C. 102(b) as being anticipated by Shah et al., Cell 85:331-343, May 3, 1996.

Shah et al., teach mRNA analysis of neural crest cells which are immortalized to the extent that they are capable of multipotent proliferation, and are differentiated to smooth muscle cells. The cells thus inherently express SM22α in a quantity and time sufficient for induction of

smooth muscle differentiation. The cells have been shown to increase expression of BMP-2 and MASH1 genes as measured by in situ hybridization and immunohistochemistry, see in particular Figure 1, and SMA, calponin, see in particular Figure 4. Thus, the reference teachings anticipate the claimed invention.

13. Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., US Patent 5,672,499 filed June 7, 1995 and issued September 30, 1997.

Anderson et al., US Patent 5,672,449 teach O cells which are smooth muscle cells derived from immortalized neural crest cells and which are recognized to differentially express smooth muscle actin, desmin and calponin in comparison to precursors or neural stem cells differentiated to neurons or glia, as evidenced by antigen expression, see in particular abstract and Example 10. Thus these cells inherently differentially express mRNA for muscle associated molecules. In addition, the cells inherently express SM22α in a quantity and time sufficient for induction of smooth muscle differentiation. Thus, the reference teachings anticipate the claimed invention.

14. Claim 7 is rejected under 35 U.S.C. 102(e) as being anticipated by Anderson et al., US Patent 6,001,654 filed April 25, 1997 and issued Dec. 14, 1999.

Anderson et al., US Patent 6,001,654 teach O cells which are smooth muscle cells derived from immortalized neural crest cells and which are recognized to differentially express smooth muscle actin, desmin and calponin in comparison to precursors or neural stem cells differentiated to neurons or glia, as evidenced by antigen expression, see in particular abstract and Example 10. Thus these cells inherently differentially express mRNA for muscle associated molecules. In

addition, Anderson teach the desire to delineate those factors which direct the propagation and differentiation of such stem cells to neuronal or smooth muscles cells, see in particular column 18, line 26-column 19, line 8. In addition to the aforementioned molecules differentiated smooth muscle cells are recognized to differentially express MASH1, see in particular Example 11. In addition, the cells inherently express SM22α in a quantity and time sufficient for induction of smooth muscle differentiation. Thus, the reference teachings anticipate the claimed invention.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 7-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shah et al., Cell 85:331-343, May 3, 1996, Anderson et al., US Patent 5,672,499 filed June 7, 1995 and

issued September 30, 1997, Anderson et al., US Patent 6,001,654 filed April 25, 1997 and issued Dec. 14, 1999, Baetscher et al., US Patent 5,922,601 filed Sep. 16, 1996 and issued July 13, 1999, and Liang et al., US Patent 5,599,672 filed Dec. 8, 1994 and issued Feb. 4, 1997.

Shah et al., teach mRNA analysis of neural crest cells which are immortalized to the extent that they are capable of multipotent proliferation, and are differentiated to smooth muscle cells. The cells thus inherently express SM22α in a quantity and time sufficient for induction of smooth muscle differentiation. The cells have been shown to increase expression of BMP-2 and MASH1 see in particular Figure 1, and SMA, calponin, see in particular Figure 4.

Anderson et al., US Patent 5,672,449 teach O cells which are smooth muscle cells derived from immortalized neural crest cells and which are recognized to differentially express smooth muscle actin, desmin and calponin in comparison to precursors or neural stem cells differentiated to neurons or glia, as evidenced by antigen expression, see in particular abstract and Example 10. Thus these cells inherently differentially express mRNA for muscle associated molecules. In addition, the cells inherently express SM22α in a quantity and time sufficient for induction of smooth muscle differentiation.

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addition, Anderson teach the desire to delineate those factors which direct the propagation and differentiation of such stem cells to neuronal or smooth muscles cells, see in particular column 18, line 26-column 19, line 8. In addition to the aforementioned molecules differentiated smooth muscle cells are recognized to differentially express MASH1, see in particular Example 11. In addition, the cells inherently express SM22α in a quantity and time sufficient for induction of smooth muscle differentiation.

Shah and Anderson et al do not explicitly teach the identification of genes which are up-regulated or down-regulated by differential display.

Baetscher et al., US Patent 5,922,601 teach methods of determining regulated genetic loci in a population of cells, see in particular abstract. In addition Baetscher et al teach differential display as taught by Liang and Pardee 1992 and Liang et al., 1993. Baetscher et al., teach the importance of these approaches for identifying and characterizing regulated genes in particular for identifying genes regulated during differentiation. In addition, Baetscher et al., teach the applicability of such methods to study a family of master regulatory genes identified in the cellular lineage of skeletal muscle differentiation.

Liang et al., US Patent 5,599,672 teach differential display and subsequent cloning of mRNA molecules from different populations of cells in order to determine regulated genetic loci, see in particular abstract and Use of invention, columns 12-13.

Thus, it would have been prima facie obvious to the skilled artisan as motivated by Baetscher and Liang to study the up and down-regulation of genes in *in vitro* culture systems

which have been shown to possess genetic loci which are differentially expressed as in the differentiated muscle cells of Shah or Anderson et al as set forth above utilizing the modified technology of either Baetscher et al or Liang et al. One of skill in the art would expect success using such methods given the high skill in the art for the manipulation and cloning of genes using recombinant DNA cloning, PCR technology and the method of differential display.

Status of Claims

17. No claims are allowed.

18. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
August 14, 2000

Gary L. Kunz
GARY L. KUNZ
SUPERVISORY PATENT EXAMINER
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